

RESEARCH ETHICS

Proceeding with clinical trials of animal to human organ transplantation: a way out of the dilemma

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The transplantation of porcine organs to humans could in the future be a solution to the worldwide organ shortage, but is to date still highly experimental. Further research on the potential effects of crossing the species barrier is essential before clinical application is acceptable. However, many crucial questions on efficacy and safety will ultimately only be answered by well designed and controlled solid organ xenotransplantation trials on humans. This paper is concerned with the question under which conditions, given the risks involved and the ethical issues raised, such clinical trials should be resumed. An alternative means of overcoming the safety and ethical issues is suggested: willed body donation for scientific research in the case of permanent vegetative status. This paper argues that conducting trials on such bodies with prior consent is preferable to the use of human subjects without lack of brain function.

humans which can be called successful. While a few transplantations of porcine islet cells and fetal neuronal cells have taken place during the past ten years, immunological adverse reactions of xenograft organs have limited the best survival rates of recipients to a few months (excluding two exceptional cases of nine month survival).⁴

For this reason, along with the fact that in the past several questionable clinical trials have been conducted (including Leonard Bailey's controversial transplantation in 1984 of a baboon heart into a newborn infant, known as Baby Fae),⁵ the procedure has often appeared in a bad light. In past attempts to override the cross species barrier, xenotransplantation researchers have had to deal with a long list of objections. These include objections based on religious constraints, current legislation, emotional aversion, the rights and welfare of animals, the financial interests of stakeholders, uncertainties concerning the safety of the procedure, and the high costs that are involved. Although all of these problems are important, we will limit ourselves to questions regarding the safety of the procedure, as this is to date the main challenge to progress in the clinical application of solid organ xenotransplantation. We will argue that experimenting on permanent vegetative status (PVS) bodies with prior consent has important advantages with regard to safety and ethical issues. This proposal is based on existing proposals regarding the use of organs from PVS bodies for transplantation purposes.

Safety issues

Over recent years, most medical attention has been focused on problems in overcoming immunological barriers. Genetic manipulation of suitable source animals is thought to be capable of eliminating the relevant porcine genes or adding the necessary human genes, so as to deceive the human immune system from activating hyperacute rejection.⁶ Recent studies suggest that hyperacute rejection is slowly being resolved by immunosuppression modalities and the production of alpha-1,3-galactosyltransferase knock-out pigs by homologous recombination.⁷ Nevertheless, there are other forms of rejection which still need to be overcome: acute humoral xenograft rejection and acute cellular xenograft rejection,⁸ in both of which the pathogenesis is not yet fully known. Several researchers believe that these forms of rejection can be overcome by

According to the Eurotransplant International Foundation—the second largest organ procurement system in the world—the demand for organ transplantation continues to grow at 15% per year.¹ It is said that the increase will persist because of the shortage of human donors and the fact that improved technical skills and anti-rejection medication make transplantation an advisable treatment for more and more disorders. The lengthening waiting lists have compelled experts to search for an unlimited source of organs for transplantation. According to some, this is exactly what xenotransplantation has to offer in the near future.

“Xenotransplantation” refers to the practice of transplanting, implanting, or infusing living cells, tissues, or organs from one species to another. The term can also imply the *ex vivo* contact of bodily fluids, cells, or tissues between different species (for example, liver bridges).² In what follows, we will mainly address xenotransplantation as the transplantation of a solid organ graft from pigs to humans for orthotopic (life saving) use.

To date, the procedure is still highly experimental, although the first serious attempts go back to the beginning of the twentieth century, when Mathieu Jaboulay transplanted the first vascularised renal xenografts.³ However, there have as yet not been any experiments of solid organ xenotransplantation conducted on

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new immunosuppressive agents or by additional genetic modification of the source animals; so far this has not been established. In addition, many physiological incompatibilities between the widely divergent species remain largely unexplored⁹ and are yet another series of problems that remain uninvestigated. It is thus still highly questionable if a genetically engineered porcine organ will one day support the life of a human.

Moreover, ever since Patience *et al* provided evidence that variants of porcine endogenous retrovirus (PERV) could infect human cells,¹⁰ the issue of potential transmission of infectious agents to a human recipient has repeatedly been raised in discussions on safety. Proof has been gathered of in vitro co-culture human cell line infection by at least three variants of the provirus¹¹ and recent studies have elicited infection of certain non-human primate cells.¹² Furthermore, one in vivo model has been shown prone to PERV infection.¹³ On the contrary, in vivo studies in non-human primate models showed no evidence of PERV infection.¹⁴ More importantly, no proof exists to date of humans infected after limited exposure to porcine cells,^{15–18} although persistent microchimerism has been shown many years after exposure.¹⁹

At present, few data address the degree of risk for a new viral infection through xenotransplantation. Recent research does seem to point out that this risk is lower than previously thought.^{20–21} Extensive lists²² have been designed of possible pathogens resulting from a xenograft implant, and sensitive assays²³ have been developed to detect potential endogenous and exogenous viruses that may remain in the carefully bred specified pathogen free swine. Nevertheless, some scientists have stressed that one can never be certain as to whether or not an organ is carrying a dangerous virus, due to the fact that some viruses may be unfamiliar, or latently present.²⁴ The post-xenotransplantation infection results already obtained are mainly acquired from tests on isolated cells—no long term survival of a whole organ xenotransplantation model in humans has been obtained—and are thus restricted. Therefore the peril of unleashing a new epidemic through xenotransplantation remains. The fact that the techniques sought to prevent xenograft rejection lower the barrier for transmission of disease²⁵ and that genetic modification of pigs may cause adaptation of the animal viruses²⁶ support this fear. It has also been argued that the complete removal of PERV via selective breeding and knock-out technologies is difficult, as multiple copies are present in the genomic DNA of all porcine cells.²⁷

Moving ahead

Both in the UK and USA, oversight agencies are nevertheless increasingly eager to continue with research concerning xenotransplantation. It is indeed conceivable that we are overestimating the magnitude of the problem. As we cannot currently predict the consequences of transplantation of a transgenic porcine organ into a human, we must also bear in mind the possibility that no transmission of dangerous, uncontrollable viruses will occur. In this case, many would find it immoral to deny such a life saving intervention if it is one day thought feasible. It would be questionable to still allow transplant teams to increasingly rely on problematic strategies to widen the donor pool, such as the use of organs from so called marginal donors. The use of organs from elderly donors²⁸ and donors with a health condition^{29–30} is not an attractive alternative to the prospect of transplanting compatible, healthy porcine organs. Safe and effective xenotransplantation would not only resolve the current allograft shortage, it would also annul the high financial and emotional burdens associated with long waiting times for an available donor organ and allow for a precisely

scheduled transplant, thereby overcoming many practical problems for the transplant team. Also, specially engineered pigs may one day provide suitable organs for infants, for whom the organ shortage is the most devastating.

Proceeding with limited xenotransplantation trials and experiments involving human subjects

Research restricted to tests on infected human blood samples in controlled laboratories cannot cover all possible consequences that viruses may have on living human bodies. This is also the case for in vivo animal models, although these are instructive opportunities for basic research. Even trials on non-human primates, although assumed to produce the most convincing results due to the great genetic similarities with humans, cannot produce conclusive results given the fact that both species react differently to certain viruses, and that their immunosuppression is less well understood than that of humans. Large scale use of primates as experimental subjects is also ethically very problematic, precisely because of the great similarity with humans, not only genetic but also at a cognitive and emotional level.

Further progress in pre-clinical studies is necessary before clinical trials of solid organ xenografts are considered. Nevertheless, it is well established that many crucial questions on efficacy and safety, including those regarding the side effects of immunosuppressive drugs, the presence of infection, and features involving the physiological interaction between the xenograft organ and the host, will ultimately only be answered by well designed and controlled solid organ xenotransplantation trials on humans.³¹ In what follows, we examine the question of under which conditions, given the risks and ethical issues involved, such clinical trials should be resumed in due time.

SUGGESTION

Living human subjects

Proceeding with limited experimentation and trials on human subjects will ultimately be the inevitable step in order to investigate the consequences that improved xenotransplantation technique may have on a human body. Although this research must ultimately rest on experimentation involving living human subjects, this is not an ideal starting point. As the Council of Europe has recently suggested, such clinical experimentation must first have evident therapeutic benefit to the recipient and must exclude all risks to public health.³²

In the case of xenotransplantation, it is conceivable that certain individual transplant patients, facing death, will express their voluntary willingness to participate in new clinical trials of xenotransplantation even if therapeutic benefit is not fully established. As future trial recipients may have little chance of surviving if they are not given an alternative to allotransplantation, they will probably find the unknown consequences of the xenotransplant acceptable. However, such a situation would be most problematic.

For one, as the risk of unleashing a pandemic outweighs the benefits to the individual recipients, this would violate one of the most basic medical norms requiring a balance between the predictable risks and burdens and foreseeable benefits to the subject or to others.³³ Moreover, some extreme measures would be required in order to protect public health, and some of these conflict with the rights of human experimental subjects as well as some basic human rights. Because of the ill defined risks, future experimental xenograft recipients will have to consent to possible constraints of monitoring and to precautionary measures which restrict social and personal contact. Minimally, the first new recipients will be asked to permit long term monitoring, along with indefinite testing and preservation

of samples.³⁴ Attempts to trace and study possible unknown viruses—let alone to control real outbreaks—are however lacking when limited to collecting blood and tissue samples. Most guidelines therefore include the prerequisite that relevant contacts must be informed about the experimental subject's status of xenograft recipient, above all those who are submitted to possible contact with their bodily fluids. Especially cautious measures will have to be met with respect to behaviour towards sexual partners, who will probably be required to undergo regular testing as well. The recipients will perhaps also be advised against having children. In extremis, if contagious infection does occur, the surveillance could go as far as placing the experimental subjects in solitary confinement for an indefinite time, allowing almost no exposure at all.³⁵

Even with the awareness that precautionary measures of this sort are necessary from the perspective of public health matters, it is hard to see how such drastic measures may be imposed on the subjects. That many of the suggested restrictions are difficult to justify is an opinion articulated in an early report by the Nuffield Council.³⁶ When considering some of the harsher constraints, the recipient is not merely inflicted with the physical risks of infection and of immunological harms, but also with a denial of significant psychological interests. At stake here are intrusions of the right to non-interference in personal affairs and private life, the protection of confidential information, and—in the theoretical case of isolation—the right to liberty. Violations to these rights are deemed justifiable by the Council of Europe in the interests of public safety.³⁷ Nevertheless, such measures would undoubtedly cause psychological and social harm to the recipient—and conceivably also to the close contacts in his or her social environment—while ideally the interests of the research subjects are the prime consideration.

Furthermore, problems arise concerning informed consent. Firstly, in no way can the recipients be fully informed of the possible consequences of the experiment, due to the unforeseeable and unquantifiable threat. Secondly, the voluntariness of participation can be questioned due to the despair the patients are driven by. Also, it is not unthinkable that the patient might disagree with his former consent over time. The consequences of a participant's decision to withdraw from the research after the experiment—a basic right formulated in the Declaration of Helsinki³⁸—would be drastic. Finally, the requirement of consent is complicated enough regarding individual patients; in this case it would call for plural consent from close contacts, and possibly even public consent. Although attempts of achieving public consent have recently been made,³⁹ it is clearly quite hard to attain for individual experimental cases of xenotransplantation.

In summary, xenotransplantation trials on living human subjects would intrude upon generally accepted ethical codes and rights regarding experimentation on humans, which can all be grasped by the norm that the physician must “(...) protect the life, health, privacy, and dignity of the human subject.”⁴⁰ Presuming that the alternative to xenotransplantation is a valuable one, however, the concern about the loss of the substantial knowledge that could be gained from experimental trials must remain. Future clinical trials of xenotransplantation must first and foremost be safe and conform with ethical principles. If this is not feasible, alternative means of obtaining information about human bodily reactions to long term xenograft exposure are a necessity. In what follows, we attempt to explore and examine the possibilities of experimenting with human subjects who can neither be harmed by the side effects of the experiment nor be an infectious hazard to others.

Living human bodies

From a research perspective, the most instructive situation would enable the acquisition of sufficient data from non-therapeutic experiments on biologically active human bodies. From an ethical perspective, on the contrary, the need to protect the physical and psychological well being of the subjects and the broader community is of paramount importance. Given these discordant interests, experiments should ideally be conducted on humans who, although alive in the biological sense, do not suffer from health risks or restrictions on their personal and social life. This means that the ideal research subjects should lack the essential aspects of human existence to which human rights and medical-ethical principles are attributed, while they are nonetheless biologically active.

In this respect it could be argued that such living bodies are comparable with the bodies of the brain dead, and one could thus suggest the use of brain dead bodies as research subjects. Brain dead bodies—living cadavers, as they were once called⁴¹—are bodies with total loss of brain function that are connected to a mechanical ventilator in an intensive care unit thereby sustaining some somatic functioning. Conducting xenotransplantation experiments on the whole brain dead is conceivable, as it is technically possible to transplant porcine organs in such bodies, while the basic bodily functions—such as breathing and steady blood flow—are artificially maintained. From an ethical point of view, this would be an attractive situation because it would enable complete examination of the xenotransplantation effects. It would also drastically minimise the risks of contagion from possible viruses, as the bodies experimented on could be quarantined for an indefinite time. This situation would be preferable to the use of living patients in that a brain dead body, lacking the sentience of its biological existence, cannot suffer from the otherwise psychologically distressing constraints nor from the physical consequences of the transplantation. Research would evidently benefit, as the experiments could increase our understanding of potential viral infections and immunological reactions without putting the population at risk. This advantage could be optimised if it were then decided to halt all other trials of xenotransplantation until the results of these small scale trials were evaluated.

There are however practical problems with such a scenario. With whole brain death, relatively no significant bodily function will work on its own. The techniques used to keep basic bodily functions working may prove sufficient to keep organs and tissues from deteriorating, yet they do not ensure a relatively normal bodily reaction to the xenograft. Moreover, the mechanical devices designed to keep the body biologically active cannot continue doing so indefinitely, perhaps not long enough to ensure the absence of latent viruses.

Are the ideal experimental subjects of the sort described, then, purely theoretical? One cannot help but think of patients who are in a permanent vegetative state (the very word “vegetative” implying that these are bodies in such mere biological existence), a state that can last for many years until it results in biological death.

The vegetative state is a clinical condition—thus defined by Jennet and Plum⁴²—of profound brain damage, characterised by loss of awareness with preserved arousal. In the literature, there is not much clarity on the term as the distinction between vegetative state, persistent vegetative state, and permanent vegetative state is often neglected. The Multi-Society Task Force on PVS has attempted to provide us with better delineated stipulation, employing the term “persistent” to describe patients vegetative for more than one, three, or 12 months, according to aetiology; whereas the term

“permanent” is used to imply the irreversibility of the condition.⁴³ It is this latter meaning, characterised by irreversible abolition of consciousness, which we wish to address here.

With the term “*Permanent Vegetative State*” (PVS), we refer to a state in which *all* functioning of the cerebral cortex—the core of consciousness—is *permanently* lost, and yet the brain stem (or parts of it) is still working. It is characterised by preserved autonomic and vegetative functions despite irreversible mental impairment. Reflex motor actions such as spontaneous eye opening, yawns, chewing, and grimacing still occur, as well as spontaneous respiration and physiologic features of sleep and wakefulness. Nevertheless, a patient having lapsed into a PVS lacks awareness and cognition which is apparent in, for example, the inability of purposeful, voluntary, and reproducible responses to stimulation.⁴⁴ Precise information on the prevalence of PVS is lacking, but studies show that the condition occurs fairly regularly. Estimates indicate that in the USA alone there are between 10 000 to 25 000 adults and between 4000 to 10 000 children in PVS.⁴⁵

Due to the fact that spontaneous breathing and reflex motor actions remain present, it is counterintuitive to think of these patients as dead. At present, our society emphasises the irreversible cessation of all brain functions as the main criterion for diagnosing death. However, debate on this criterion has been ongoing since the standard of whole brain death was proposed by the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death in 1968.⁴⁶ Robert Veatch was a pioneer in challenging the need of total lack of brain function and emphasised the importance of sentient and socially interactive existence.⁴⁷ No proposals concerning a higher brain death criterion have been legally endorsed as of yet and therefore a patient in PVS is still statutory a living patient. Still, one could argue that even the term “patient” is inappropriate in relation to the condition, because the word generally refers to a living person, while a body in PVS has permanently lost all forms of personhood. Regardless of the ongoing dispute on what constitutes personhood, to be a person at minimum requires the capacity for cognitive and affective mental functioning, which is inextricably bound with the notion of awareness. The parts of the brain that are crucial in terms of the mind and to sentient existence are irreversibly lost in a PVS body. The organism can no longer experience pain and pleasure or any other feelings, does not have any awareness of the environment or the self, and has no capacity for information integration. PVS bodies have no interest in maintaining their biological life, nor do they value it, as they have permanently lost the capacity to acquire values. That is in fact the idea behind former case specific court approvals for the removal of feeding tubes: they acknowledge the fact that the PVS body has no interests in treatments it may or may not receive. Likewise, one could argue, it is of no interest to a PVS body whether or not the body is engaged in clinical xenotransplantation trials as it can neither benefit from the advantages nor suffer from the disadvantages that are associated. Having no capacity for any mental activity whatsoever and thus left in a state of complete unconsciousness, it is reasonable to say that in fact a PVS body has no interests at all, a rationale often rehearsed in the literature.

Of course, the idea we are suggesting here is not entirely new. Over the past years, some philosophers have defended the opinion to legalise the use of organs from cortically dead bodies for transplantation.⁴⁸ Commentators have argued that it is “intrinsicly moral” to use the organs of anencephalic neonates, who lack functioning cerebral hemispheres, as this would allow some good to come from their tragic situation.⁴⁹ They claim that the lives of other children could be

maintained, while at the same time meaning given to the short and non-sentient existence of the anencephalics. In fact, this position was taken by the AMA Council on Ethical and Judicial Affairs as early as 1988.⁵⁰ Several philosophers apply similar argumentations in favour of organ retrieval from PVS bodies, once the decision has been made to allow these bodies to die through withdrawal of all treatment.⁵¹ The arguments appealed to are based on a conviction that such bodies are irreversibly non-sentient and non-cognitive, and thus have no interest in being biologically maintained, whereas their organs could save the lives of many.

Regardless of the intention of the authors, one could logically derive from their suggestion concerning retrieval of organs for transplantation purposes the idea that it is permissible to treat PVS bodies the way we currently treat the bodies of the whole brain dead. Based on the idea that PVS—if established that the decisive brain damage is permanent—implies the death of the person, we are of the opinion that not only the donation of organs but of the entire body for scientific research should be permissible for PVS bodies on the condition that former consent has been obtained. Moreover, while potential organ donations from PVS bodies would increase the amount of donor organs available, they will still fall short in meeting demand and will thus be of limited value. On the other hand, the implications of willed body donation in case of cortical death for xenotransplantation related research are far reaching. As the autonomic and vegetative functions of PVS bodies can often be maintained for years, their use would allow the opportunity to fully test the long term consequences of a solid organ xenotransplantation, which will contribute to the progress necessary before large scale clinical application to unlimited potential recipients can be considered.

DISCUSSION: THE UNBEARABLE LIGHTNESS OF NOT BEING

The suggestion offered here raises several questions. Ultimately, it is about consented donation of the body to science in the case of cortical brain death. In our view, the following main concerns remain: (1) the need for certain diagnosis of the irreversibility of the state; (2) the need for sufficient and relevant functioning of a body in PVS; (3) the need for prior and informed consent by the person ending up as a PVS body.

(1) The problem of establishing the irreversibility of loss of cognitive capacity is often cited. Although diagnostic certainty of cortical brain death is an indisputable prerequisite of our suggestion, dispute exists over the ability of scientific medicine to achieve this certainty. PVS is taken to be essentially permanent three months after non-traumatic and twelve months after traumatic brain injury.⁵² However, single case reports exist of recovery with moderate disability after non-traumatic PVS lasting eighteen months and traumatic PVS lasting for thirty six months.⁵³ Recent research suggests that therapies can be designed to induce patients to emerge from PVS.⁵⁴ There is still disagreement over whether exceptional cases of “awakening” are due to a lack of diagnostic certainty or whether these were just incidents of misdiagnosis. It is indeed a challenge to ensure complete and irreversible loss of capacity for consciousness, because the diagnosis depends on providing evidence of a negative, an absence. However, beyond a certain point, hope for bringing back the most rudimentary form of consciousness is gone. New techniques are constantly being developed to specify that point with accuracy. Positron emission tomography,⁵⁵ and studies on the magnetic resonance of the brain,⁵⁶ among others, are important efforts in understanding the neural processes underlying the vegetative state. If in the future such techniques prove to be reliable, then we could be certain

that the experiments we are suggesting would be limited to bodies that are demonstrably irreversibly cortically destroyed.

(2) A second possible obstacle to the realisation of our proposal is that it may be discovered that a body in PVS, and in particular the immune system, does not sufficiently function like a normal body with unaffected brain functioning. If so, there is no reason to prefer our scenario to the use of animal models, as neither approach would attain the compelling conclusions on the safety of the procedure. However, at present there is no clarity on this. Were this to be the case, then our suggestion would indeed be useless within the framework of xenotransplantation trials, although it would still make sense for many other forms of scientific research.

(3) If it can be agreed upon that PVS bodies can be regarded as dead, then experimenting on them is legitimate under the same conditions as experiments on cadavers. Training and refining invasive technical skills on cadavers or newly deceased patients is not an uncommon practice in medicine due to a lack of suitable educational alternatives for these procedures. Multiple surveys have shown that the general public does not disapprove of this method.⁵⁷ It is generally deemed ethically acceptable when perceived as an educational opportunity which will benefit many patients dependent on the technical, lifesaving skills practiced. However, as a substantial prerequisite of all scientific research on human bodily material, former consent would be necessary to ensure that the experiments are not conducted against the personal wishes of the deceased person. Registering a “living will” is a means of ensuring that the right to self determination is respected after death.

An additional argument in favour of allowing the donation of one's PVS body for scientific experimentation can be drawn from some people's refusal to grant that a cadaver and a dead person may be treated alike. Over the past century, we have gone a long way before acknowledging that whole brain death (also formerly described as “hopelessly unconscious patients”)⁵⁸ is a sufficient condition of death of the individual. However, much controversy over the legitimacy of this concept still exists today. It has been suggested that the concept of death is not inextricably bound with the criteria of whole brain death. Debate exists, for instance, on the equation of brain death to the cessation of integrated functioning of the entire body.⁵⁹ There is also evidence that weakens the idea that there is a total absence of all brain function at the moment “whole brain death” is determined.⁶⁰ Moreover, and in contrast with what the term presumes, the declaration of whole brain death is in medical practice often based on the irreversible cessation of particular brain functions, while other brain activity—deemed irrelevant in deciding whether one is dead or alive—remains. Rather, it is the death of the brainstem that is the decisive criterion, because all higher brain activity is assumed to be dependent on lower brain activity (and this suggests that there is a tendency to think less of the lower brain functions in terms of defining life, and to emphasise the critical role of the higher, cortical forms).

It seems that there is still much conflict about what constitutes death even among experts. Because convictions about death are not absolute, one might argue that in the end it should be left to the individual himself to choose the criterion/criteria of death he or she wishes to endorse in a living will. This idea was formerly formulated by Robert Veatch: he proposed to legally tolerate religious and philosophical objections to a uniform definition of death, “(...) a conscientious objection that permits patients to choose, while competent, an alternative definition of death provided that it is within reason and does not pose serious public or other societal concerns.”⁶¹ Veatch argues that it goes

against the fundamentals of liberal pluralism to prevent individuals with dissenting religious and philosophical views from incorporating other definitions of death.

With regard to our suggestion, a testamentary will relating to postmortem research is required, allowing an individual to indicate the concept(s) that best corresponds to the individual's own concept of death (be it cardiopulmonary, whole brain, or cortical brain death). Such a will would also allow a person—keen to help science—to stipulate his or her wish to donate the body or certain bodily materials to science in accordance with that concept of death. In the latter case, one could (should one desire) specify the type of research he or she wants to participate in. In this way, one could for example opt to participate in the xenotransplantation trials discussed. Information could be provided to instruct those interested in the different types of research and the consequences they will have on the body. Perhaps such a deliberately expressed wish could be recorded on identification documents or in a whole body donor registry.

Some important questions remain when considering allowing people to donate their body to science in accordance with individual conceptions of death.

Firstly, it may be put forward that the general public will not welcome such a shift in policy. If permitting willed body donation in case of PVS implies that we go against some of the most fundamental convictions on life and death matters held by relatives, physicians, and the general public, our suggestion could cause public distrust and outrage. However, studies on public attitudes show conflicting evidence. On the one hand, reports on organ donation indicate continued discomfort among respondents—including physicians—over the equation of whole brain death with the death of the patient.⁶² On the other hand, several studies suggest rather unconventional attitudes towards cortical brain death. One American study showed that 89% of respondents thought it ethical to withdraw life prolonging treatment in cases of PVS; almost two thirds held that it is ethical to use the organs of PVS bodies.⁶³ Aside from this, no consensus on what constitutes death is required in order to implement our suggestion, as the emphasis is on personal beliefs.

Secondly, it may be suggested that conducting experiments on PVS bodies is disrespectful of the deceased person, because invasive procedures and mutilating treatments would be applied. However, such experimentation on cadavers is deemed acceptable under certain circumstances. If similar conditions are met in the case of PVS and if prior consent is legitimate, experimenting on PVS bodies is no more disrespectful than current postmortem research. Also, assuming that a deceased person has no interests (our argument for allowing experimentation to be conducted on PVS bodies in the first place), one could conclude that a PVS body similarly has no interests in whether or not its prior wishes are respected. Deciding to acknowledge the personal wishes as expressed in a will in spite of this, speaks in favour of respect for the dead. Moreover, whole body donation of this kind is not just respectful of the wishes of the deceased, but also promotes other values, because use is made of the body to increase medical knowledge and help others.

A final issue concerns the question of whether decisions regarding the scientific and medical use of the body are ultimately restricted to the person who died, or if relatives or other parties involved are entitled to decide. This is a topical concern. Recent literature, for instance, reports that most adults believe that consent from family members prior to practicing procedures on the newly dead is advisable.^{64–65} New Zealand is one country that has legally enforced the right of a formal family veto to override the deceased's directive in relation to retention of body parts.⁶⁶ The arguments emphasise the enduring interests of others after death. It is

important to consider the effect PVS body donation would have on the family. With regard to our suggestion, one could indeed claim that while the suffering of the PVS body may not be at stake, the relatives are emotionally involved in the way the body is treated and, as such, should have a say in the matter as well. As a PVS body is not a corpse ready for burial, it is conceivable that conducting experiments on it will be very distressing to them.

When considering the interests of relatives, a similarity as well as a distinction can be drawn between donation of a cadaveric body and of a PVS body for scientific purposes. Both practices are comparable in that the disposal of the bodily remains is uncertain. This implies that either the two practices should be equally condemned, or equally permitted. The main difference, however, lies in the fact that the scientific or medical use of the warm bodies of deceased persons (higher cortical or whole brain death) evokes entirely different emotional reactions compared with the use of a "cold" cadaver.

In spite of this emotional distress, there are many cases where the testamentary wishes of an individual take priority over the emotional involvement of the family. In many countries, for instance, advance directives concerning end of life decisions (both refusal of treatment and—as in Belgium and the Netherlands—request for actively ending the life) of patients who become permanently or even irreversibly unconscious are respected regardless of the objections of relatives. As persons who are irreversibly unconscious or "dead" no longer have any interests, one could in principle argue that testaments—of any kind—have no stringent power. Nevertheless, it is generally accepted that the transfer of property and patrimony, and of wishes concerning end of life decisions or preferences with regard to burial, are arranged according to the terms of a will. The precise intention of having a will is to ensure that an individual's wishes are followed, even if that person no longer has a stake in his wishes being followed because he no longer exists in that sense. In the case of PVS body donation, relatives may even be helped by the fact that the deceased has stipulated his wish to body donation in case of cortical death. They may be consoled by the altruistic nature of the donation and by the fact that body donation is something the deceased deliberately chose.

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